Application Type	BLA
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Division / Office	DECPT/OTAT
Committee Chair	Zuben Sauna, Ph.D.
Clinical Reviewer(s)	Megha Kaushal, MD
Project Manager	Niloofar Kennedy
Priority Review	Yes
Reviewer Name(s)	Jiang Hu, Ph.D.
Review Completion Date / Stamped Date	
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Applicant	Bioverativ Therapeutics Inc
Established Name	Efanesoctocog alfa
(Proposed) Trade Name	ALTUVIIIO
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Antihemophilic Factor (Recombinant), Fc-Von Willebrand Factor-XTEN Fusion Protein
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for solution for intravenous injection
Dosing Regimen	50 IU/kg once weekly for routine prophylaxis; 50 IU/kg x 2 (IU/dL per IU/kg) for on-demand treatment and control of bleeding episodes and perioperative management
Indication(s) and Intended Population(s)	Indicated in adults and children with hemophilia A (congenital factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes, (2) On demand treatment & control of bleeding episodes, (3) Perioperative management of bleeding.

Table of Contents

GLOSSARY

ABR	Annualized bleeding rate
AE	Adverse event
AESI	Adverse Events of Special Interest
AJBR	Annualized joint bleeding rate
aPTT	Activated partial thromboplastin time
AsBR	Annualized spontaneous bleeding rate
BLA	Biologics License Application
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical study report
eCRF	Electronic case report form
ED	Exposure day
FAS	Full analysis set
FVIII	Coagulation factor VIII
GCP	Good Clinical Practive
HEAD-US	Hemophilia early arthropathy detection with ultrasound
HJHS	Hemophilia joint health score
IND	Investigational New Drug
IR	Information Request
ISTH	International Society on Thrombosis and Hemostasis
IV	Intravenous
PGA	Physician's global assessment
PK	Pharmacokinetic
PKAS	PK Analysis Set
PPS	Per Protocol Set
PTP	Previously treated patient
QoL	Quality of life
QW	Once weekly
rFVIII	recombinant FVIII
SAE	Serious adverse event
SAS	Safety Analysis Set
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
VWF	Von Willebrand factor

1. Executive Summary

This original Biologics License Application (BLA) is submitted for ALTUVIIIO, an antihemophilic (recombinant), FC-von Willebrand factor-XTEN fusion protein indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes; (2) On-demand treatment and control of bleeding episodes; (3) Perioperative management of bleeding.

This BLA is supported by the completed phase 3 pivotal Study EFC16293, the on-going phase 3 pediatric Study EFC16295, and the on-going phase 3 long term Study LTS16294.

In Study EFC16293, the following key efficacy results were observed for ALTUVIIIO among subjects 12 years of age and older:

1. A total of 86 bleeding episodes were observed and treated in the prophylaxis arm, in which 133 previously treated patients (PTPs) with severe hemophilia A were enrolled and received ALTUVIIIO at 50 IU/kg once weekly for 52 weeks. The mean annualized bleeding rate (ABR) estimated through a negative binomial model was 0.71 with 95% confidence interval (CI) of (0.52, 0.97). The upper bound of the CI of the estimated ABR was lower than the pre-specified threshold of 6, demonstrating effective protection against bleeds in weekly prophylaxis with ALTUVIIIO.
2. There were 362 bleeds treated with 375 injections of ALTUVIIIO in this study, 350 (96.7%) bleeding episodes were controlled with a single injection, and 11 (3.0%) were controlled with 2 injections. The hemostatic efficacy in treatment of bleeds was rated by the subjects as excellent or good in 317 (84.5%) of 375 injections.

For safety, no inhibitor development to FVIII was observed in this study.

In Study EFC16295, a total of 67 pediatric PTPs with severe hemophilia A were enrolled into 2 cohorts by age (<6 years of age and 6 to <12 years) and the primary endpoint was the occurrence of inhibitor development to FVIII. Although no inhibitor development to FVIII was detected with the interim data submitted to the BLA, all of the subjects had fewer than 50 EDs (primary analysis population), therefore precluding the evaluation of the primary safety objective pre-specified in the protocol. The ABRs were evaluated in 23 subjects (11 in the < 6 years cohort and 12 in the 6 to<12 years cohort) with an efficacy period of at least 26 weeks. The overall estimated mean ABRs were 0.54 (95% CI: 0.23, 1.26) for treated bleeding episodes, and 3.6 (95% CI: 1.6 to 8.4) for all bleeding episodes, as of the interim data cutoff. Because the sample size for ABR analysis at the interim analysis was small (one third of the planned sample size), the representativeness of the population may be questionable, therefore impacting the reliability of the study results.

For the perioperative management of bleedings, 12 major surgeries were treated in Study EFC16293, 1 major surgery was treated in Study EFC16295, and 8 major surgeries were treated in Study LTS16294. The hemostatic response was rated as excellent by the investigators/surgeons in all 21 major surgeries.

One death occurred in Study EFC16293 due to pancreatic carcinoma metastatic. This death was assessed by the investigator as not related to ALTUVIIIO.

Overall, the statistical analyses provided adequate evidence to support the efficacy and safety of ALTUVIIIO in all three indications for use in adults and adolescents (12 years of age and older). However, data evidence from the interim analyses of the ongoing Study EFC16295 for children less than 12 years of age was limited and incomplete. At this stage I am unable to support the conclusion of safety in terms of inhibitor development for this population and defer to the clinical reviewer on the adequacy of the interim data of Study EFC16295 in supporting the indication in the pediatric population.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is an X-chromosome linked bleeding disorder that occurs predominantly in males and is characterized by a deficiency of functional coagulation factor VIII (FVIII) leading to life-threatening bleeding in response to trauma and recurrent spontaneous bleeding into soft tissue and joints.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indications

Treatments for hemophilia A require replacement with a form of FVIII. All currently marketed FVIII replacement products bind to endogenous von Willebrand factor (VWF) and are thus subject to a half-life ceiling of approximately 15 to 19 hours. ALTUVIIIO is a VWF-independent FVIII replacement therapy and it provides sustained FVIII activity levels with weekly dosing.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

ALTUVIIIO is the first recombinant FVIII (rFVIII) protein specifically designed to be independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII-VWF interactions.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

ALTUVIIIO was evaluated in clinical trials under Investigational New Drug (IND) application 17464. It received Orphan Drug status in the US for the treatment of Hemophilia A on 03 August 2017.

The FDA granted ALTUVIIIO fast track designation on 05 February 2021 for the treatment of hemophilia A and breakthrough therapy on 13 May 2022 for the

treatment of Hemophilia A in adults and children 12 years of age and older. The applicant's request for the proprietary name ALTUVIIIO was submitted through IND 17464/106 and was conditionally accepted by FDA on 02 November 2021.

The FDA granted the applicant's request for a rolling submission as noted in the FDA Type B Pre-BLA Meeting Responses dated 25 May 2022 (CRMTS13983). BLA Part 1 of 2 was submitted on 12 May 2022 (SN0001) and included all nonclinical documents.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The statistical memo focuses on the two phase 3 studies, the pivotal phase 3 study EFC16293 in adult and adolescent PTPs and the pediatric phase 3 study EFC16295 in PTPs <12 years of age. The individual study was reviewed in section 6, and the integrated efficacy of perioperative management of bleeding across studies EFC16293, EFC16295, and LTS16294 was reviewed in section 7.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents in BLA 125771 were reviewed and served as the basis for this statistical memo:

- 125771/0001
  - Module 1
- 125771/0002
  - Module 2.2: Introduction
  - Module 2.5: Clinical overview
  - Module 2.7: Clinical summary
  - Module 5.3.5.2: Clinical study reports, protocols, and SAPs for EFC16293, EFC16295
  - Module 5.3.5.3: Pooled analyses of efficacy and safety of all studies
  - Datasets of single studies and pooled datasets

This memo also reviewed the amendment 125771/0/22 received by CBER on 12/23/2022 in response to FDA's information request (IR) sent on 12/2/2022, as well as the amendment 125771/0/37 received by CBER on 2/16/2023 in response to FDA's IR sent on 2/15/2023.

5.3 Table of Studies/Clinical Trials

The clinical program comprised seven clinical studies, including three phase 3 studies (EFC16293, EFC16295, LTS16294), two phase 1/2a studies (242HA101, 242HA102), and two phase 1 studies (PKM17085, PKM16978). Among the seven clinical studies, six studies enrolling subjects with severe hemophilia A, and one study (PKM16978) enrolling subjects with von Willebrand disease.

Three early phase studies were conducted for subjects with severe hemophilia A: a dose escalation Study 242HA101, a multiple dose Study 242HA102 to assess the safety and pharmacokinetics (PK) of ALTUVIIIO, and a PK study PKM17085 to characterize the PK profiles of ALTUVIIIO. There are two phase 3 studies: the pivotal Phase 3 Study EFC16293 in adult and adolescent PTPs and the pediatric Phase 3 Study EFC16295 in PTPs <12 years of age. There is also an on-going long-term extension Study LTS16294.

A summary of all seven studies is provided in Table 1.

Table 1: Summary of clinical studies supporting ALTUVIIIO registration

Study Code	***Study Description***	***Number of Participants***	***Dosing Regimen and Treatment Duration***	***Population***	***Status***
EFC16293 Phase 3 Pivotal	Open-label study to assess the safety, efficacy, and PK of ALTUVIIIO in PTPs with severe hemophilia A, ≥12 years of age.	159 (133 in Arm A; 26 in Arm B)	50 IU/kg once weekly for 52 weeks (Arm A) 50 IU/kg on-demand for 26 weeks followed by a switch to 50 IU/kg once weekly for 26 weeks (Arm B)	Adult and adolescent PTPs with severe hemophilia A (≥12 years of age)	Completed
EFC16295 Phase 3 Pediatric	Open-label study to assess the safety, efficacy, and PK of ALTUVIIIO in pediatric PTPs with severe hemophilia A, <12 years of age.	Planned: 65 Enrolled as of cut-off date: 67 (31 in <6 years of age cohort; 36 in 6 to <12 years of age cohort)	50 IU/kg once weekly for 52 weeks	Pediatric PTPs with severe hemophilia A (<12 years of age)	Ongoing
LTS16294 Phase 3 Long term study	Open-label study to assess the long-term safety and efficacy of ALTUVIIIO in PTPs with severe hemophilia A. In addition, 2 separate openlabel arms with patients newly initiated on ALTUVIIIO in China; and patients who are planned to undergo major surgery.	Planned: 262 (215 who roll over from Ph3; 37 Chinese participants in Arm B; up to 10 major surgery participants in Arm C). Enrolled as of cut-off date: 159 (123 in Arm A; 32 in Arm B; 4 in Arm C).	50 IU/kg once weekly Up to 48 months (Arm A) 52 weeks (Arm B and Arm C)	PTPs with severe hemophilia A (all ages)	Ongoing

Study Code	***Study Description***	***Number of Participants***	***Dosing Regimen and Treatment Duration***	***Population***	***Status***
242HA101 (TDU16220) Phase 1/2a	Open-label, dose escalation, safety, tolerability, and PK of a single IV dose of ALTUVIIIO.	16 (7 in the low dose cohort; 9 in the high dose cohort)	25 IU/kg (low dose cohort) 65 IU/kg (high dose cohort) Single dose	Adult PTPs with severe hemophilia A (18 to 65 years of age)	Completed
242HA102 (TDR16219) Phase 1/2a	Open-label, safety, tolerability, and PK repeat-dose study of ALTUVIIIO.	24 (10 in Cohort 1; 14 in Cohort 2)	50 IU/kg (Cohort 1) 65 IU/kg (Cohort 2) 4 once weekly doses	Adult PTPs with severe hemophilia A (18 to 65 years of age)	Completed
PKM17085 Phase 1	Open-label, Phase 1, 3-period fixed sequence study to assess PK profiles of ALTUVIIIO, SHL and EHL rFVIII after a single IV injection in males	13	50 IU/kg Single dose	Adult PTPs with severe hemophilia A (18 to 65 years of age)	Completed
PKM16978 Phase 1	Open-label, Phase 1, multicenter, single-arm study to characterize the PK of ALTUVIIIO after a single IV injection and to assess safety, and tolerability of ALTUVIIIO in adult participants	Planned: 9 Enrolled as of cut-off date: 5	25 IU/kg Single dose	Adult male and/or female patients with type 2N or 3 VWD (18 to 65 years of age)	Ongoing

Source: Adapted from BLA 125771/0 Module 2.5: clinical-overview.pdf, Table 1, page 15-17.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study EFC16293

6.1.1 Objectives

The primary objective of Study EFC16293 was to evaluate the efficacy of ALTUVIIIO as a prophylaxis treatment.

Secondary study objectives included:

- To evaluate the efficacy of ALTUVIIIO as a prophylaxis treatment (using other endpoints than the primary endpoint)
- To evaluate the efficacy of ALTUVIIIO in the treatment of bleeding episodes
- To evaluate ALTUVIIIO consumption for the prevention and treatment of bleeding episodes
- To evaluate the effect of ALTUVIIIO prophylaxis on joint health outcomes
- To evaluate the effect of ALTUVIIIO prophylaxis on Quality of Life (QoL) outcomes
- To evaluate the efficacy of ALTUVIIIO for perioperative management
- To evaluate the safety and tolerability of ALTUVIIIO treatment
- To assess the PK of ALTUVIIIO based on the one-stage activated partial thromboplastin time (aPTT) and (b) (4) chromogenic FVIII activity assays

6.1.2 Design Overview

This was a multinational, multicenter, open-label Phase 3 study to evaluate the safety, efficacy, and PK of ALTUVIIIO in PTPs ≥12 years of age with severe hemophilia A.

There were two arms in this study:

- Arm A included subjects who were on a prophylaxis treatment regimen with FVIII prior to the study. Subjects in Arm A were to receive ALTUVIIIO at a dose of 50 IU/kg IV once weekly on a prophylaxis treatment regimen for up to 52 weeks. Approximately 124 subjects were planned to be enrolled in Arm A.
- Arm B included subjects who were on an on-demand treatment regimen prior to the study. Approximately 26 subjects were planned to be enrolled in Arm B and receive ALTUVIIIO as:
  - On-demand regimen: Subjects in Arm B received ALTUVIIIO at a dose of 50 IU/kg IV as on-demand treatment of bleeding episodes for the first 26 weeks

  followed by:
  - Prophylaxis regimen: Subjects in Arm B switched to receive ALTUVIIIO at a dose of 50 IU/kg IV once weekly as a prophylaxis treatment regimen for another 26 weeks.

6.1.3 Population

Subjects enrolled in this study were PTPs with

- severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A)
- aged 12 years or older
- subjects from Arm B (on-demand regimen) had to have at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment
- Previous treatment for hemophilia A (prophylaxis or on-demand regimen) was defined as any treatment with any recombinant and/or plasma derived FVIII product, or cryoprecipitate for at least 150 exposure days (EDs).

Subjects with a history of a positive inhibitor test or with a positive inhibitor test result at Screening were excluded.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For prophylaxis, subjects received a weekly dose of 50 IU/kg IV.

For on demand treatment, a single dose of 50 IU/kg IV was applied for all bleeding episodes. If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days might be considered. For minor/moderate bleeding episodes occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose might also be used.

For perioperative management, single dose of 50 IU/kg IV was administered for all subjects. Additional doses of 30 or 50 IU/kg every 2 to 3 days might be administered for major surgery.

6.1.6 Sites and Centers

The study was conducted worldwide in 19 countries/regions (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Spain, South Korea, Taiwan, UK, and USA) at 51 centers. Subjects were enrolled from 48 of the 51 centers.

6.1.7 Surveillance/Monitoring

Study centers were monitored by the Contract Research Organization (CRO) according to CRO procedures. Centers were visited at regular intervals and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with Good Clinical Practice (GCP); and the completeness, accuracy, and consistency of the data. Direct access to subject medical and laboratory records was permitted to verify entries on the study specific Case Report Forms (CRFs).

6.1.8 Endpoints and Criteria for Study Success

Efficacy Endpoints

The primary efficacy endpoint is annualized bleeding rate (ABR). The ABR for each individual subject was calculated as: 365.25 × (number of treated bleeding episodes during the efficacy period) / (total number of days during the efficacy period). All types of treated bleeding episodes (spontaneous, traumatic, and type unknown) were included in determining the ABR.

Secondary efficacy endpoints to evaluate the efficacy of ALTUVIIIO as a prophylaxis treatment include:

- Intra-patient comparison of ABR during the ALTUVIIIO weekly prophylaxis treatment period versus the historical prophylaxis ABR for subjects in Arm A who participated in study 242HA201/OBS16221 (key secondary endpoint).
- ABR by type and location for prophylaxis treatment per study arm.
- ABR for all bleeding episodes (including untreated bleeding episodes) for prophylaxis treatment per study arm.
- Intra-patient comparison of ABR during the once weekly (QW) prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B.
- Percentage of subjects who maintain FVIII activity levels over 1%, 5%, 10%, 15%, and 20% in Arm A.

Secondary efficacy endpoints to evaluate the efficacy of ALTUVIIIO in the treatment of bleeding episodes include:

- Number of injections and dose of ALTUVIIIO to treat a bleeding episode per study arm and treatment regimen.
- Percentage of bleeding episodes treated with a single injection of ALTUVIIIO per study arm and treatment regimen.
- Assessment of response to ALTUVIIIO treatment of individual bleeding episodes based on the International Society on Thrombosis and Hemostasis (ISTH) 4-point response scale per study arm and treatment regimen.
- Physician’s global assessment (PGA) of subject’s response to ALTUVIIIO treatment based on a 4-point response scale per study arm and treatment regimen.

Secondary efficacy endpoints to evaluate the efficacy of ALTUVIIIO for perioperative management include:

- Investigators’ or Surgeons’ assessment of subject’s hemostatic response to ALTUVIIIO treatment on the ISTH 4-point response for surgical procedures scale.
- Number of injections and dose to maintain hemostasis during perioperative period for major surgery.
- Total ALTUVIIIO consumption during perioperative period for major surgery.
- Number and type of blood component transfusions used during perioperative period for major surgery.

- Estimated blood loss during perioperative period for major surgery.

Safety Endpoints
Safety endpoints include:

- The occurrence of adverse events (AEs) and serious adverse events (SAEs).
- The occurrence of clinically significant changes from baseline in physical examination, vital signs, and laboratory tests.
- Development of inhibitors (neutralizing antibodies directed against factor VIII [FVIII]) as determined via the (b) (4) Bethesda assay.
- The occurrence of embolic and thrombotic events.

Success Criterion
The study was to be deemed as a success and the weekly prophylaxis treatment regimen would be considered to provide adequate bleeding control if the upper bound of the exact one-sided 97.5% confidence interval of ABR using a negative binomial model is less than or equal to 6. This success criterion was considered acceptable given the ABR variability based on the marketed FVIII products at the time of protocol development.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size determination
The sample size was estimated to rule out a greater-than-acceptable risk of immunogenicity. Assuming a drop-out rate of approximately 15%, a sample size of 124 subjects in the prophylaxis arm was expected to provide 104 evaluable subjects with at least 50 EDs. Specifically, 104 subjects were to provide at least 90% power for testing the upper bound of the 95% CI is less than 6.8% (a threshold for inhibitor development determined at the FDA Factor VIII Inhibitor Workshop in 2003). If ≤ 2 subjects out of 104 evaluable subjects develop an inhibitor, the upper bound of an exact 95% confidence interval would exclude 6.8%.

Based on 2000 simulations of a negative binomial regression model with mean ABR of 2.9 and dispersion factor of 2.3, a sample size of 124 subjects were to provide at least 90% power for the upper bound of the 95% CI to exclude an ABR greater than 6.

For the key secondary efficacy endpoint, to test the null hypothesis (median difference in ABR exceeds or is equal to noninferiority margin) versus the alternative hypothesis (median difference in ABR is less than noninferiority margin), a sample size of 63 achieves 90% power to detect non-inferiority using a one-sided paired Wilcoxon Signed-Rank test at a 0.025 significance level when the actual mean of paired differences is 0 and the non-inferiority margin is 4. The superiority will also be tested when non-inferiority is achieved. Superiority can be declared if the upper bound of the one-sided 97.5% confidence interval is less than 0. In order to account for drop-out and the use of the Per Protocol Set, a

total of at least 75 subjects who have completed at least 6 months of participation in observational study will be enrolled in Arm A.

Reviewer's Comment:
The power calculation for the key secondary efficacy endpoint was based on a nonparametric method (Wilcoxon Signed Rank test). This method is different than the primary method pre-specified in the statistical analysis plan (SAP) which compares the mean ABRs using a negative binomial regression model.

Analysis Populations
The All-Enrolled Analysis Set include all subjects who were enrolled in the study, regardless of whether they were dosed with study drug or not.

The Full Analysis Set (FAS) include all subjects who received at least one dose of study drug. All analyses of demographics, baseline characteristics, and efficacy were based on the FAS.

The Per Protocol Set (PPS) is a subset of the FAS including subjects who did not have important protocol deviations potentially impacting efficacy. The Per Protocol Set was utilized for analysis of the key secondary efficacy endpoint, as well as sensitivity analysis of the primary endpoint.

The Safety Analysis Set (SAS) was the same as the full analysis set and included all subjects who receive at least one dose of study drug. All analyses of safety were based on the Safety Analysis Set, unless otherwise specified.

Primary Efficacy Analyses
The primary analysis of the primary endpoint estimated the mean ABR and one-sided 97.5% CI using a negative binomial model for the weekly prophylaxis arm (Arm A) based on the FAS.

The key secondary endpoint, the intra-subject comparison of ABR between ALTUVIIIO weekly prophylaxis and historical prophylaxis, were performed using a negative binomial regression model accounting for overdispersion with the dependent variable as "total bleeding episodes", covariate as "treatment regimen", repeated variable as "subject", and log time as an offset variable. The mean paired difference and 95% CI were estimated using the PPS (as primary analysis) and FAS (as supportive analysis).

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 170 subjects were screened, 11 (6.5%) of whom were screen failures. A total of 159 subjects were enrolled: 133 in Arm A and 26 in Arm B. All the subjects received at least one dose of ALTUVIIIO. Table 2 summarizes analysis population information.

Table 2: Analysis Populations

	Arm A Prophylaxis	*Arm B On-demand*	*Arm B Prophylaxis*	*Overall*
Full analysis set	133	26	26	159
Safety analysis set	133	26	26	159
Per-protocol set	129	26	25	154

Source: Adapted from BLA 125771/0 Module 5.3.5.1: EFC16293-16-18-body.pdf, Table 6, page 31.

6.1.10.1.1 Demographics

A summary of demographic and baseline characteristics is provided in Table 3.

The mean (SD) age of the subjects was 35.4 (15.1) years (range: 12 to 72 years); 25 (15.7%) subjects were between 12 and 17 years, 129 (81.1%) were between 18 and 64 years and 5 (3.1%) were 65 years or older. Adolescents aged 12 to 17 years old were all in Arm A. One female subject was enrolled; all other subjects were male. Four geographic regions were represented in the study with half of the subjects enrolled in Europe, specifically: Europe (81 [50.9%] subjects), Asia/Pacific (33 [20.8%] subjects), North America (26 [16.4%] subjects), and South America (19 [11.9%] subjects).

Table 3: Summary of demographic and baseline characteristics (FAS)

	Arm A N=133	*Arm B N=26*	*Surgery Subgroup N=13*	*Overall N=159*
Age (year)				
Mean (SD)	33.9 (15.3)	42.8 (11.7)	44.3 (12.8)	35.4 (15.1)
Median	34.0	39.0	46.0	35.0
Min; Max	12; 72	23; 68	12; 64	12; 72
Age group				
12 - 17	25 (18.8)	0	1 (7.7)	25 (15.7)
18 – 64	104 (78.2)	25 (96.2)	12 (92.3)	129 (81.1)
≥ 65	4 (3.0)	1 (3.8)	0	5 (3.1)
Sex				
Male	132 (99.2)	26 (100)	13 (100)	158 (99.4)
Female	1 (0.8)	0	0	1 (0.6)
Ethnicity				
Hispanic or Latino	12 (9.1)	13 (50.0)	1 (7.7)	25
Not Hispanic	112 (84.8)	13 (50.0)	9 (69.2)	125
Not reported due to confidentiality	8 (6.1)	0	3 (23.1)	8
Not known	1	0	0	1
Race				
Asian	29 (21.8)	0	3 (23.1)	29 (18.2)
Black of African American	3 (2.3)	0	0	3 (1.9)
White	71 (53.4)	26 (100)	7 (53.8)	97 (61.0)
Not reported due to confidentiality	26 (19.5)	0	3 (23.1)	26 (16.4)
Other	4 (3.0)	0	0	4 (2.5)
Region				
Asia/Pacific	33 (24.8)	0	4 (30.8)	33 (20.8)
Europe	67 (50.4)	14 (53.8)	5 (38.5)	81 (50.9)
North America	26 (19.5)	0	3 (23.1)	26 (16.4)
South America	7 (5.3)	12 (46.2)	1 (7.7)	19 (11.9)
BMI (kg/m^2)				
Mean (SD)	25.59 (5.00)	26.91 (5.56)	25.68 (1.50)	25.68 (1.50)
Median	25.51	26.35	25.47	25.74
Min; Max	15.0 ; 39.8	16.7 ; 40.8	22.6 ; 28.4	15.0 ; 40.8
BMI group				
< 25	57 (42.9)	9 (36.0)	3 (23.1)	66 (41.8)
25 - 30	52 (39.1)	9 (36.0)	10 (76.9)	61 (38.6)
≥ 30	24 (18.0)	7 (28.0)	0	31 (19.6)

Source: Adapted from BLA 125771/0 Module 5.3.5.1: EFC16293-16-18-body.pdf, Table 8, page 35-36.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
At study entry, all subjects had a documented FVIII activity level below 1% or a documented genotype known to produce severe hemophilia A. The median and mean (SD) age at start of first prophylaxis were 1.0 and 3.6 (6.0) years for subjects in Arm A. For 25 of 26 subjects in Arm B who were on on-demand treatment for at least 150 EDs before study entry, the age at start of first prophylaxis was reported (median of 3.0 and mean [SD] of 10.8 [15.1] years) indicating these subjects had been on prophylaxis treatment earlier in life. All subjects had at least 150 prior EDs to FVIII.

The majority of the subjects (125 [78.6%]) had no family history of a FVIII inhibitor.

6.1.10.1.3 Subject Disposition
Thirteen subjects (12 in Arm A and 1 in Arm B) were included in the surgery subgroup and 2 subjects (both in Arm A) had major surgery after their last dose of ALTUVIIIO and were thus not taken into account in the assessments of major surgeries.

Five subjects (4 in Arm A and 1 in Arm B) with important protocol deviations potentially impacting efficacy were not included in the PPS. There was one subject, in Arm A, whose study participation was impacted by COVID-19 (failure to conduct study visit at Week 39 because of COVID-19) therefore this subject was reported as a major protocol deviation.

A total of 149 (93.7%) subjects completed the study and 10 (6.3%) prematurely discontinued. In Arm A, 9 subjects discontinued due to the following reasons:

- 3 for prohibited concomitant medication
- 3 for consent withdrawn
- 1 adverse event (AE) of CD4 lymphocytes decreased
- 1 protocol violation
- 1 other reason related to the subject’s personal situation

In Arm B, one subject died because of pancreatic cancer with multiple metastatic nodules in liver.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

In the FAS, a total of 86 treated bleeding episodes were observed and treated with ALTUVIIIO in 133 subjects who had an efficacy period in Arm A. The total follow-up was 121.2 subject-years. The mean ABR estimated from the negative binomial model was 0.71 (95% CI: 0.52 to 0.97) in Arm A. The upper limit of the 1-sided 97.5% CI was substantially less than the prespecified value of 6, demonstrating that the weekly prophylaxis treatment regimen with ALTUVIIIO provided effective protection against bleeds.

The median (Q1; Q3) ABR was 0.00 (0.00; 1.04). During the study, 86 (64.7%) subjects had no bleeding episodes and 131 (98.5%) subjects had 5 or fewer episodes per year.

Of the 133 subjects in Arm A from the FAS, 129 were included in the PPS and 128 subjects had an efficacy period of at least 26 weeks. Results of the sensitivity analysis on the PPS and subjects with an efficacy period of at least 26 weeks were consistent with the results of the primary analysis. The mean ABR estimated with the negative binomial model in the PPS was 0.72 (95% CI: 0.53 to 0.98) in Arm A. For 128 subjects with an efficacy period of at least 26 weeks, the mean ABR estimated with the negative binomial model was 0.66 (95% CI: 0.48 to 0.91) for all treated bleedings.

Table 4 summarizes the analysis for treated ABRs for both FAS and PPS.

Table 4: Summary of Treated ABR in Arm A

	Primary analysis (FAS)	*Sensitivity analysis (PPS)*
Number of PTPs	133	129
Total number or treated bleeding episodes	86	86
Total subject-year followed	121.2	120.3
Mean (SD) of ABR	0.71 (1.43)	0.74 (1.45)
Median of ABR (Q1, Q3)	0.00 (0.00, 1.04)	0.00 (0.00, 1.04)
Mean of ABR, model based (95% CI)	0.71 (0.52, 0.97)	0.72 (0.53, 0.98)
Subjects who had 0 bleeding (%)	86 (64.7)	82 (63.6)

Source: Adapted from BLA 125771/0 Module 5.3.5.1: CSR for Study EFC16293, Table 13 and Table 16.2.6.1.3

6.1.11.2 Analyses of Secondary Endpoints

Intra-subject comparison of ABR between ALTUVIIIO weekly prophylaxis and historical prophylaxis (key secondary endpoint)

Subjects who had an efficacy period ≥ 26 weeks in study EFC16293 and had an observation period ≥ 26 weeks in study OBS16221 were included in the analysis. There were 78 subjects in the FAS and 77 in the PPS.

In the PPS, there were 212 treated bleeding episodes with 69.7 subject-years follow-up in study OBS16221 while there were 51 treated bleeding episodes with 73.5 subject-years follow-up in EFCEFC16293. The non-inferiority of prophylaxis treatment with ALTUVIIIO over historical prophylaxis on mean ABR was demonstrated in the PPS as the upper bound of the 1-sided 97.5% CI of the

difference between ALTUVIIIO prophylaxis and historical prophylaxis (estimated mean difference in ABR: -2.30 with 95% CI [-3.49, -1.11]) was below the prespecified non-inferiority margin of 4 bleeds per year. The superiority of ALTUVIIIO prophylaxis treatment over historical prophylaxis was then tested and demonstrated in the prespecified hierarchical step-down testing procedure in the FAS (upper bound of the 1-sided 97.5% CI of the ABR ratio between ALTUVIIIO prophylaxis and historical prophylaxis was less than 1 [rate ratio: 0.23 with 95% CI of 0.13 to 0.42])

Reviewer's comment: The applicant submitted detailed data for the observational study OBS16221. However, there was no description of the study in the form of study protocol or clinical study report, which precluded a thorough review and assessment of any potential bias due to study design.

Overview of Annualized Spontaneous Bleeding Rate (AsBR)
In Arm A, there were 33 spontaneous bleeding episodes, resulting in the estimated mean AsBR as 0.27 (95% CI: 0.18 to 0.41). There were 107 subjects (80.5%) had no spontaneous bleeds and no subjects had spontaneous bleeding episodes greater than 5. In Arm B, there were 197 and 5 spontaneous bleeding episodes in on-demand regimen and prophylaxis regimen respectively, showing that the estimated mean AsBR decreased after subjects switched to prophylaxis treatment (0.44 [95% CI: 0.16 to 1.20]) as compared to on-demand treatment (15.83 [12.27 to 20.43]). With on-demand treatment, 21 subjects (80.8%) had an AsBR greater than 5 for spontaneous bleeds and 7 subjects (26.9%) had an AsBR greater than 20; after switching to prophylaxis treatment, 22 subjects (84.6%) had no spontaneous bleeds, and no subjects had an AsBR greater than 5.

Overview of Annualized Joint Bleeding Rate (AJBR)
In Arm A, 37 subjects had a total of 61 treated joint bleeds. The mean AJBR estimated from the negative binomial model was 0.51 (95% CI: 0.36 to 0.72). In Arm B, 26 subjects had 219 joint bleeds in the on-demand regimen and 5 subjects had 7 joint bleeds in the prophylaxis regimen. The estimated mean AJBR was lower after switching to prophylaxis treatment (0.62 [95% CI: 0.25 to 1.52]) as compared to on-demand treatment (17.48 [95% CI: 14.88 to 20.54]).

Overview of ABR for All Bleeding Episodes
In Arm A, the estimated mean ABR based on all bleeding episodes, i.e., treated and untreated, was 1.11 (95% CI: 0.83 to 1.48). For subjects with an efficacy period of at least 26 weeks, the mean ABR based on all bleeding episodes was 1.04 (95%CI: 0.78, 1.39). In Arm B, the estimated mean ABR based on all bleeding episodes was 22.21 (95% CI: 19.41 to 25.42) with on-demand treatment and 0.88 (95% CI: 0.42 to 1.84) when participants switched to prophylaxis treatment.

Number of injections and dose of ALTUVIIIO to treat a bleeding episode

In total, across the 2 treatment arms, 362 bleeds were treated with ALTUVIIIO. Analysis per bleeding episode showed that all but 1 of the bleeding episodes (99.7%) were controlled with ≤ 2 injections of ALTUVIIIO, with 350 (96.7%) controlled by only 1 injection. No bleeding episode required more than 3 injections.

Assessment of subjects' response to ALTUVIIIO treatment of bleeding episodes
Overall, across the 2 treatment arms, 375 injections of ALTUVIIIO were given to treat 362 bleeding episodes during the efficacy period. Of these injections, 334 were evaluated for response with the majority (94.9%) rated by the subjects as excellent or good.

Perioperative (surgical) management
A total of 14 major surgeries were performed in 13 subjects, including 12 from Arm A and 1 from Arm B. One subject (Subject (b) (6)) underwent 2 major surgeries (hip replacement on Day 37 and neurolysis of the ulnar nerve on Day 164). Two major surgeries (osteosynthesis of right tibia in Subject (b) (6) and coronary artery bypass in Subject (b) (6)) took place after the last ALTUVIIIO dosing and are excluded from the assessments of major surgeries. Therefore, only 12 major surgeries were included in the assessment of hemostatic response. Hemostatic response was rated as excellent by the Investigators/Surgeons for all 12 major surgeries, supporting the effectiveness of ALTUVIIIO in perioperative management. Eleven out of 12 major surgeries required a single injection of ALTUVIIIO.

6.1.11.3 Subpopulation Analyses

Subgroup analyses of the mean treated ABR were performed on the FAS. The treatment effects were consistent across subgroups defined by age categories, bleeding phenotype at baseline, number of target joints at screening or dosing and dosing interval compliance, confirming the primary endpoints. For each participant, the efficacy period reflects the sum of all intervals of time during which participants were treated with ALTUVIIIO excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days). Table 5 summarizes the subgroup analyses of treated ABRs.

Table 5: Summary of treated ABRs by subgroup - FAS

	Sample size	*Mean ABR*	*95% CI*
Age group			
12-17 years	25	0.26	(0.11; 0.57)
18-64 years	104	0.84	(0.60; 1.17)
≥ 65 years	4	0.34	(0.05; 2.38)
Bleeding phenotype at baseline*			
0	44	0.31	(0.18, 0.54)
>0-5	57	0.83	(0.51; 1.34)
>5-10	14	1.26	(0.70; 2.27)
>10	7	1.84	(0.51; 6.63)
Number of target joints at screening			
None present	107	0.68	(0.48; 0.96)
≤ median	17	1.16	(0.55; 2.47)
>median	9	0.27	(0.07; 1.09)
Dosing and dosing interval compliance*			
Both dose and interval compliant	131	0.72	(0.53; 0.98)
Dose compliant but interval not compliant	1	NC	(NC, NC)
Interval compliant but dose not compliant	0	NC	(NC, NC)
Neither dose nor interval compliant	0	NC	(NC, NC)

*: The sample size includes participants with an efficacy period in each subgroup.
Source: Adapted from BLA 125771/0 Module 5.3.5.1: EFC16293-16-18-body.pdf, Figure 3, page 51.

6.1.12 Safety Analyses

6.1.12.3 Deaths

There was one death in Arm B. This subject ((b) (6)) had a medical history of HCV and died on Day 217 of pancreatic carcinoma metastatic. The death was reported as a TESAE on Day 173 and was assessed by the investigator as not related to ALTUVIIIO.

6.1.12.4 Nonfatal Serious Adverse Events

Of the 159 subjects in the SAS, 15 (9.4%) experienced a total of 18 treatment-emergent serious adverse event (TESAEs). In Arms A and B, 16 TESAEs were reported in 13 (9.8%) subjects and 2 TESAEs were reported in 2 (7.7%) subjects, respectively.

6.1.12.5 Adverse Events of Special Interest (AESI)

AESIs included development of inhibitors, Grade 3 or higher allergic reactions or anaphylactic reactions (per CTCAE Version 5.0), and embolic or thrombotic events (except for injection site thrombophlebitis). Inhibitor development to FVIII was defined as a neutralizing antibody value ≥ 0.6 Bethesda unit (BU)/mL confirmed by a second test result of ≥ 0.6 BU/mL from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn.

There were no reports of inhibitor development to FVIII, no reports of Grade 3 or greater allergic reactions or anaphylaxis in association ALTUVIIIO administration, and no reports of embolic and thrombotic events during this study either.

6.1.12.7 Dropouts and/or Discontinuations

Two treatment-emergent adverse events (TEAEs) in 2 (1.3%) subjects resulted in permanent discontinuation of treatment:

- Subject (b) (6) with a history of HIV infection experienced a TESAE of CD4 lymphocytes decreased on Day 92 that was assessed by the Investigator as severe and related to ALTUVIIIO. No corrective treatment was given, and the event did not resolve following treatment discontinuation.
- Subject (b) (6) had a TESAE of combined tibia-fibula fracture on Day 14 that was assessed by the Investigator as moderate and not related to ALTUVIIIO. The event was considered resolved on Day 18. Study drug was discontinued following use of another FVIII product (prohibited medication).

6.2 Trial #2: Study EFC16295

6.2.1 Objectives

The primary objective of Study EFC16295 was to evaluate the safety of ALTUVIIIO in previously treated pediatric subjects with hemophilia A.

Secondary objectives included:

- To evaluate the efficacy of ALTUVIIIO as a prophylaxis treatment
- To evaluate the efficacy of ALTUVIIIO in the treatment of bleeding episodes
- To evaluate ALTUVIIIO consumption for the prevention and treatment of bleeding episodes
- To evaluate the effect of ALTUVIIIO prophylaxis on joint health outcomes

- To evaluate the effect of ALTUVIIIO prophylaxis on QoL outcomes
- To evaluate the efficacy of ALTUVIIIO for perioperative management
- To evaluate the safety and tolerability of ALTUVIIIO treatment
- To assess the PK of ALTUVIIIO based on the one-stage aPTT and (b) (4) (b) (4) chromogenic FVIII activity assays

6.2.2 Design Overview

This was a multinational, multicenter, open-label Phase 3 study to evaluate the safety, efficacy and pharmacokinetics of ALTUVIIIO in PTPs <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII).

The study was composed of two age cohorts of children (<6 years and 6 to <12 years), and subjects received ALTUVIIIO at a dose of 50 IU/kg IV once weekly for 52 weeks. There were 67 subjects enrolled in order to achieve at least 50 subjects (25 subjects <6 years of age and 25 subjects 6 to <12 years of age) completing approximately 52 weeks of treatment to obtain at least 50 exposure days.

6.2.3 Population

Subjects enrolled in this study were PTPs with severe hemophilia A aged younger than 12 years. Previous treatment of hemophilia A (prophylaxis or on-demand) was defined as any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs for patients aged 6-11 years and for at least 50 EDs for patients aged <6 years. Subjects with a history of a positive inhibitor test or with a positive inhibitor result at screening were excluded.

6.2.4 Study Treatments or Agents Mandated by the Protocol

For prophylaxis, subjects received a weekly dose of 50 IU/kg IV.

For on demand treatment, a single dose of 50 IU/kg IV was applied for all bleeding episodes. If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days might be considered. For minor/moderate bleeding episodes occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose might also be used.

For perioperative management, single dose of 50 IU/kg IV was administered for all subjects. Additional doses of 30 or 50 IU/kg every 2 to 3 days might be administered for major surgery.

6.2.6 Sites and Centers

Subjects were screened at 39 study centers and enrolled from 37 study centers in 15 different countries (USA, Canada, France, Germany, Hungary, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, UK, Turkey, Australia, and Taiwan).

6.2.7 Surveillance/Monitoring

The study monitoring for Study EFC16295 is similar to that of Study EFC16293. Please see section 6.1.7.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint for this study was the occurrence of inhibitor development, defined as an inhibitor result of ≥ 0.6 BU/mL. The primary analysis of inhibitor development is based on all subjects who have reached at least 50 EDs and had at least one inhibitor test performed at or beyond this milestone.

Selected secondary endpoints of Study EFC16295 include: ABR (for treated bleeding episodes), which is defined in Section 6.1.9. 6.2.9 Statistical Considerations & Statistical Analysis Plan.

Sample Size Determination
The determination of the number of subjects was based on clinical rather than statistical considerations. Taking into consideration the guideline from Committee for Medicinal Products for Human Use (EMEA/CHMP/BPWP/144533/2009 rev.2), approximately 65 PTPs were planned to be enrolled in order to obtain at least 50 subjects with at least 50 EDs at the end of the study. At least 12 subjects in each age cohort were needed to have completed adequate blood sample collection to assess key PK parameters.

Analysis Populations
The All-Enrolled Analysis Set included all subjects who were enrolled in the study, regardless of whether they were dosed with study drug or not.

The Full Analysis Set (FAS) included all subjects who received at least one dose of study drug. All analyses of demographics, baseline characteristics, and efficacy were based on the FAS.

The Per Protocol Set (PPS) was a subset of the FAS including subjects who did not have important protocol deviations potentially impacting efficacy. The Per Protocol Set was utilized for analysis of the key secondary efficacy endpoint, as well as sensitivity analysis of the primary endpoint.

The Safety Analysis Set (SAS) was the same as the full analysis set and included all subjects who receive at least one dose of study drug. All analyses of safety were based on the Safety Analysis Set, unless otherwise specified.

Statistical Analyses
For the primary endpoint, the overall incidence of positive inhibitor formation was calculated as: (Number of subjects with an inhibitor) / (Number of subjects reaching 50 EDs or who have an inhibitor). The incidence was summarized for each age cohort and overall with associated exact 95% CIs using the Clopper-Pearson method.

The secondary endpoint of ABR was analyzed using the FAS including subjects with an efficacy period of at least 26 weeks. The mean and 95% CI of ABR was estimated using a negative binomial model. The model included the number of treated bleeding episodes during the efficacy period as response variable, log-transformed duration of efficacy period as offset variable to account for variable duration.

All secondary efficacy endpoints were summarized descriptively based on the FAS and presented by age cohort and overall, unless otherwise specified. All analyses of bleeding endpoints were reported based on treated bleeding episodes, except for the summary of ABR for all bleeds which include both treated and untreated bleeds.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

At the data cut-off date for this BLA submission (24 January 2022), a total of 73 subjects were screened, among which 67 subjects were enrolled and received at least one dose of ALTUVIIIO: 31 in the <6 years of age cohort and 36 in the 6 to <12 years of age cohort. None of the subjects had completed the study. There were 23 (34.3%) subjects who reached at least 25 EDs. There were 66 subjects on-going and 1 subject withdrawn from the study.

Table 6: Analysis Populations for Study EFC16295

	< 6 years	*6 to < 12 years*	*Overall*
Full analysis set	31	36	67
Safety analysis set	31	36	67

Source: Adapted from BLA 125771/0 Module 5.3.5.1: EFC16295-16-1-8-body.pdf, Table 7, page 25.

6.2.10.1.1 Demographics

At the data cut-off date, all 67 pediatric subjects in the FAS were male.

As shown in Table 7, the mean (SD) age of subjects was 6.24 (2.93) years. In the <6 years of age cohort, the mean (SD) age was 3.72 (1.27) years (range: 1.4 to 5.0 years), and in the 6 to <12 years of age cohort, the mean (SD) was 8.42 (2.08) years (range: 6.0 to 11.0 years).

The mean (SD) weight was 17.59 (3.25) kg (range: 11.4 to 23.5 kg) for subjects aged <6 years and 35.79 (12.86) kg (range: 17.2 to 66.5 kg) for subjects aged 6 to <12 years.

Three geographic regions were represented in the study: North America (25 [37.3%] subjects), Europe (24 [35.8%] subjects), and Asia/Pacific (18 [26.9%] subjects).

Table 7: Summary of demographic and baseline characteristics (FAS)

	<6 years N=31	*6 to <12 years N=36*	*Surgery Subgroup N=1*	*Overall N=67*
Age (year)				
Mean (SD)	3.72 (1.27)	8.42 (2.08)	1	6.24 (2.93)
Median	4.0	8.0	4.0	6.0
Min; Max	1.4; 5.0	6.0; 11.0	4.0; 4.0	1.4; 11.0
Sex				
Male	31	36	1	67
Female	0	0	0	0
Ethnicity				
Hispanic or Latino	2	1	0	3
Not Hispanic	29	33	1	62
Not reported	0	2	0	2
Race				
Asian	4	4	0	8
Black of African American	0	2	0	2
White	25	25	1	50
Not reported	0	4	0	4
Other	2	1	0	3
Region				
Asia/Pacific	10	8	0	18
Europe	4	20	0	24
North America	17	8	1	25
Weight (kg)				
Mean (SD)	17.59 (3.25)	35.79 (12.86)	19.70	27.37 (13.27)
Median	18.00	32.85	19.70	22.10
Min; Max	11.4; 23.5	17.2; 66.5	19.7; 19.7	11.4; 66.5

Source: Adapted from BLA 125771/0 Module 5.3.5.1: EFC16295-16-18-body.pdf, Table 8, page 26.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
At study entry, 64 (95.5%) of the 67 enrolled subjects had a documented FVIII activity level below 1% and 3 subjects had a documented genotype known to produce severe hemophilia A. The mean (SD) age at diagnosis was 0.52 (0.82) years, ranging from birth to 4 years.

The distribution of genotypes was representative of a population with severe hemophilia A. A large proportion of subjects had genotypes associated with inhibitor development to FVIII: 12 out of 31 (38.7%) subjects had intron 22 inversions, 4 (12.9%) had missense, 4 (12.9%) had frameshift and 7 (22.6%) had other mutations. The majority of the subjects (77.6%) had no family history of an inhibitor. No subject was HIV, HBV or HCV positive.

Overall, the mean (SD) age at start of first prophylactic treatment was 1.0 (1.1) year (range 0 to 5): 53 (79.1%) subjects had prior exposure to recombinant FVIII and 14 (20.9%) subjects to plasma-derived FVIII. At time of screening, the FVIII products most frequently used were: efmoroctocog alfa (32 [47.8%] of subjects) and rurioctocog alfa pegol (12 [17.9%] subjects). Per protocol, this previously treated population had ≥50 EDs in the <6 years of age cohort and ≥150 ED in the 6 to <12 years of age cohort.

6.2.10.1.3 Subject Disposition
The SAS and FAS were composed of 67 (100%) subjects who received at least 1 injection of ALTUVIIIO. The FAS with an efficacy period included 63 (94.0%) subjects who received at least 2 prophylactic injections: 27 in the <6 years of age cohort and 36 in the 6 to <12 years of age cohort.

One subject had undergone a major surgery and a total of 4 minor surgeries had been performed before the data cut.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint of this study is the occurrence of inhibitor development. As of the data cut-off date, inhibitor development to FVIII was not detected. In all 67 treated subjects, the incidence of inhibitor development to FVIII was 0% (95% CI: 0.0, 5.4).

Reviewer's comment: At the time of data cut, none of the subjects reached at least 50 EDs, which was the pre-defined primary analysis population for the primary analysis of inhibitor incidence. Therefore, the primary objective cannot be evaluated.

6.2.11.2 Analyses of Secondary Endpoints

Overview of Annualized Bleeding Rate (ABR)

Among the 23 subjects with an efficacy period ≥ 26 weeks, 9 treated bleeding episodes occurred with 16.1 total subject-years followed. The ABR for treated bleeds estimated with a negative binomial model was 0.54 (95% CI: 0.23 to 1.26), with a median ABR of 0.00. Of the 23 subjects, 17 (73.9%) had an ABR of 0 and the other 6 (26.1%) had an ABR between 1 and 5. These 9 treated bleeding episodes were reported in 6 participants: a single bleeding episode in 2 participants in the <6 years of age cohort and in 3 participants in the 6 to <12 years of age cohort, and one participant in the 6 to <12 years of age cohort reported 4 bleeding episodes. There were 57 bleeds of all types reported for 23 subjects with at least 26 weeks of the efficacy period, resulting in the estimated mean ABR of 3.6 (95% CI: 1.6 to 8.4) and a median ABR of 0 (Q1: 0; Q3: 4.5).

Number of injections and dose of ALTUVIIIO to treat a bleeding episode
A total of 19 treated bleeding episodes (13 traumatic bleeds, 3 spontaneous bleeds and 3 bleeds of unknown etiology) were reported and treated during the efficacy period in 11 out of 63 subjects in the FAS, 3 were children under 6 years of age. Sixteen (84.2%) of the bleeding episodes were resolved with a single dose of ALTUVIIIO. All other bleeding episodes were resolved with two doses. The analysis of number of injections or dose for resolution of a bleeding episode showed consistent results in both age cohorts based on per episode or per subject to support the effectiveness of ALTUVIIIO.

Perioperative (surgical) management
One subject in the < 6 years of age cohort underwent a major surgery for extraction of a molar tooth. This subject received a preoperative (loading) dose of 61.9 IU/kg ALTUVIIIO. The hemostatic response to ALTUVIIIO was rated as excellent. There was no need of blood component transfusion during the surgical period.

6.2.11.3 Subpopulation Analyses

Subgroup analyses are performed because no inhibitor development has been observed in this on-going study.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No deaths reported during the study.

6.2.12.4 Nonfatal Serious Adverse Events

At the data cut-off date, 36 (53.7%) out of 67 subjects in the Safety Analysis Set experienced a total of 75 TEAEs: 20 (64.5%) subjects in the <6 years of age cohort experienced 40 TEAEs and 16 (44.4%) subjects in the 6 to <12 years of age cohort experienced 34 TEAEs. In the surgery subgroup, 1 TEAE was reported in 1 (100%) subject. There were no TESAEs and no TEAEs resulting in death or leading to treatment discontinuation reported.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1: Perioperative Management

In this submission, the efficacy of ALTUVIIIO in surgical prophylaxis was evaluated by combining the clinical results from three studies: EFC16293, EFC16295, and LTS16294.

As of the data cut-off date (24 January 2022), a total of 21 major surgeries were performed in 18 participants (15 adults and 3 children) using ALTUVIIIO for bleed protection during the perioperative period across the 3 Phase 3 studies, including 12 from Study EFC16293, 1 from study EFC16295 and 8 from study LTS16294. Hemostatic response for surgical procedure was rated as excellent by the investigators/surgeons for all 21 major surgeries. In addition, there were 22 minor surgeries performed in 19 subjects (12 adults and 7 children) while on ALTUVIIIO the treatment and hemostatic response was evaluated in 15 out of 22 minor surgeries, with all 15 rated as excellent.

The integrated analysis of the efficacy endpoint for surgical prophylaxis provides evidence of efficacy of ALTUVIIIO in surgical prophylaxis.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

In this memo, I reviewed the complete phase 3 pivotal Study EFC16293 and the on-going phase 3 pediatric study EFC16295. Some surgical data from the on-going phase 3 long term study LTS16294 were also included in this statistical memo.

In Study EFC16293, a total of 86 bleeding episodes were observed and treated in the prophylaxis arm, in which 133 subjects with severe hemophilia A were enrolled and received ALTUVIIIO at 50 IU/kg once weekly for 52 weeks. The mean ABR estimated through a negative binomial model is 0.71 with 95% CI (0.52, 0.97), achieving the upper bound CI of ABR lower than the pre-specified threshold 6. Overall, among 362 bleeds treated with 375 injections of ALTUVIIIO in this study, 350 (96.7%) bleeding episodes were controlled with a single injection of ALTUVIIIO, and 11 (3.0%) were controlled with 2 injections. The hemostatic efficacy in treatment of bleeds was rated by the subjects as excellent or good in 84.5% of 375 injections. The intra-participant comparison of ABR between ALTUVIIIO weekly prophylaxis and historical prophylaxis was analyzed with 77 subjects. The estimated mean difference is -2.30 with 95% CI (-3.49, -1.11), which is below the prespecified non-inferiority margin of 4 bleeds per year. No subjects developed inhibitors in the study.

In Study EFC16295, a total of 67 pediatric PTPs with severe hemophilia A were enrolled into 2 cohorts by age (<6 years of age and 6 to <12 years). The primary endpoint was the occurrence of inhibitor development to FVIII.

Although no inhibitor development to FVIII was detected with the interim data submitted to the BLA, all of the subjects had fewer than 50 EDs (primary analysis population), therefore precluding the evaluation of the primary safety objective pre-specified in the protocol. The ABRs were evaluated in 23 subjects (11 in the < 6 years cohort and 12 in the 6 to<12 years cohort) with an efficacy period of at least 26 weeks. The overall estimated mean ABRs were 0.54 (95% CI: 0.23, 1.26) for treated bleeding episodes, and 3.6 (95% CI: 1.6 to 8.4) for all bleeding episodes, as of the interim data cutoff. Because the sample size for ABR analysis at the interim analysis was small (one third of the planned sample size), the representativeness of the population may be questionable, therefore impacting the reliability of the study results.

For the perioperative management of bleedings, 12 major surgeries were treated in Study EFC16293, 1 major surgery was treated in Study EFC16295, and 8 major surgeries were treated in study LTS16294. The hemostatic response was rated as excellent by the investigators/surgeons in all 21 major surgeries.

One death occurred in Study EFC16293 due to pancreatic carcinoma metastatic. This death was assessed by the investigator as not related to ALTUVIIIO.

10.2 Conclusions and Recommendations

This original BLA proposes three indications for the ALTUVIIIO in adults and children with hemophilia A:

- Routine prophylaxis to reduce the frequency of bleeding episodes,
- On-demand treatment and control of bleeding episodes,
- Perioperative management of bleeding.

The statistical analyses provided adequate evidence to support the efficacy and safety of ALTUVIIIO in all three indications for use in adults and adolescents (12 years of age and older). However, data from the interim analyses of the ongoing Study EFC16295 for children less than 12 years of age was limited and incomplete. Without final results on the pre-specified primary analysis, I am unable to support the conclusion of safety in terms of inhibitor development in this population and defer to the clinical reviewer on the adequacy of the interim data in supporting the indication in the pediatric population.